



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

: ERYTHROCYTIC CELLS AND METHOD FOR PRESERVING CELLS

Applicant: CROWE et al. Art Unit: 1632

Serial No.: 10/052,162

Filed : January 16, 2002

Examiner: Shin-Lin Chen

Commissioner for Patents

P.O. Box 1450

Title

Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Under 35 USC §120, this application relies on the earlier filing date of application serial number 09/828,627, filed on April 5, 2001. The following references were submitted to and/or cited by the Office in the prior application and, therefore, are not provided in this application:

This statement is being filed after a first Office action on the merits, but before receipt of a final Office action or a Notice of Allowance. A check for \$180 in payment of the late submission fee of §1.17(p) is enclosed.

Respectfully submitted,

Date: October 24, 2003

CARPENTER AND KULAS, LLP 1900 Embarcadero Road

Suite 109

Palo Alto, CA 94303

Telephone: 650-842-0300

Facsimile: 650-842-0304

10/29/2003 CNGUYEN 00000141 10052162

02 FC:1806

180.00 QP

PTO 1449 (Modified)

LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION **DISCLOSURE STATEMENT** (Use Several Sheets if Necessary)

ATTORNEY DOCKET NO.	SERIAL NO.
010023-000130US	10/052,162
APPLICANT:	GROUP ART UNIT:
CROWE et al.	1632
FILING DATE:	
January 16, 2002	Page 1 of 6

			U.S. PATENT DOCU	DIMITERIA	
Examiner's Initials	Cite No.	Document Number	Publication Date (mm-dd-yyyy)	Name of Applicant	Pages, Columns, Lines Where Relevant Passages or
					Figures appear
		09/693,127	October 20, 2000		
		3,932,943	January 20, 1976	Briggs, et al.	
-		4,145,185	March 20, 1979	Brinkhous, et al.	
		4,251,995	February 24, 1981	Pert et al.	RECEIVE
		4,287,087	September 1, 1981	Brinkhous, et al.	0.86/0.51
		4,302,355	November 24, 1981	Turner, Jr., et al.	1 200
		4,585,735	April 29, 1986	Meryman, et al.	OCT 3 1 200
•		4,695,460	September 22, 1987	Holme	,
		4,717,654	January 5, 1988	Savoca et al.	TECH CENTER 160
		4,874,690	October 17, 1989	Goodrich, Jr., et al.	PALL APINIER.
•		4,880,788	November 14, 1989	Moake et al.	
		4,891,319	January 2, 1990	Roser	
		4,994,367	February 19, 1991	Bode, et al.	
		5,043,261	August 27, 1991	Goodrich, et al.	
		5,026,566	June 25, 1991	Roser	
		5,030,560	July 9, 1991	Sinor et al.	<u> </u>
		5,043,261	August 27, 1991	Goodrich, et al.	
		5,045,446	September 3, 1991	Goodrich et al.	
		5,059,518	October 22, 1991	Kortright, et al.	
		5,149,653	September 22, 1992	Roser	7
		5,151,360	September 19, 1992	Handa, et al.	
		5,153,004	October 6, 1992	Goodrich, Jr., et al.	
		5,165,938	November 24, 1992	Knighton	
		5,171,661	December 15, 1992	Goodrich, Jr., et al.	
		5,178,884	January 12, 1993	Goodrich, et al.	
		5,213,814	May 25, 1993	Goodrich, Jr., et al.	
	•	5,236,716	August 17, 1993	Carmen et al.	
		5,242,792	September 7, 1993	Rudolph, et al.	
		5,248,506	September 28, 1993	Holme, et al.	
		5,250,303	October, 5, 1993	Meryman, et al.	
-		5,328,840	July 12, 1994	Coller	****
		5,332,578	July 26, 1994	Chao	
		5,344,752	September 6, 1994	Murphy	
		5,358,844	October 25, 1994	Stossel, et al.	
		5,376,524	December 27, 1994	Murphy, et al.	
		5,378,601	January 3, 1995	Gepner-Puszkin	
		5,428,008	June 27, 1995	Chao, et al.	
		5,510,263	April 23, 1996	Quaranta, et al.	
	<u> </u>	5,651,966	July 29, 1997	Read, et al.	
		5,736,313	April 7, 1998	Spargo, et al.	
		5,827,741	October 27, 1998	Beattie, et al.	
		5,902,608	May 11, 1999	Read, et al.	
		5,958,670	September 28, 1999	Goodrich Jr., et al.	
		6,221,575	April 24, 2001	Roser et al.	i

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

PTO 1449 (Modified)	ATTORNEY DOCKET NO.	SERIAL NO.
THE TRANSMENT	010023-000130US	10/052,162
LIST OF PATENTS AND PUBLICATIONS	APPLICANT:	GROUP ART UNIT:
FOR APPLICANT'S INFORMATION	CROWE et al.	1632
DISCLOSURE STATEMENT	FILING DATE:	
(Use Several Sheets if Necessary)	January 16, 2002	Page 2 of 6

FOREIGN PATENT DOCUMENTS

Examiner's Initials	Cite No.	Foreign Patent Document	Publication Date (mm-dd-yyyy)	Name of Applicant	Pages, Columns, Lines Where Relevant Passages or Figures appear
		WO 86/03938	17 July 1986	Crowe et al.	
		WO 87/05300	11 September 1987	James et al.	
		WO 90/04329	3 May 1990	Raynor et al.	RECEIVED
		WO 93/00806	21 January 1993	Aspinall et al.	
		WO 93/14191	22 July 1993	Goodrich et al.	OCT \$ 1-200B
		WO 01/30141	03 May 2001		OCT 3 1 200
		EP0356257A2	28 February 1990	Goodrich et al.	
		EP0356257B1	29 March 1995	Goodrich et al.	TECH CENTER 1600/290
		EP0668013A2	23 August 1995	Tetsuo et al.	IPALI APINIZA

OTHER ART

<u></u>	1	OTHER ART		
Examiner's	Cite No.	Include Author, Title, Date, Pertinent Pages, Etc.		
Initials				
		ALI, et al., "Platelet Concentrates Stored for 5 Days in a Reduced Volume of Plasma Maintain		
		Hemostatic Function and Viability", The Canadian Red Cross Society and the Departments of		
		Pathology, Medicine and Clinical Epidemiology and Biostatistics, McMaster University Faculty of		
		Health Science, Hamilton, Ontario Canada, Volume 34, No. 1, 1994		
		ALLAIN et al., "Platelets Fixed with Paraformaldehyde: A New Reagent for Assay of Von		
		Willebrand Factor and Platelet Aggregating Factor", Department of Pathology, University of		
		North Carolina, J. Lab. Clin. Med., Volume 85, No. 2, pages 318-328, February 1975		
		ANDREWS et al., "Molecular Mechanisms of Platelet Adhesion and Activation," Int. J. Biochem,		
		Cell. Biol., 29(1), pp. 91-105 (1997)		
		ARGALL et al., "The Use of Trehalose-Stabilized Lyophilized Methanol Dehydrogenase from		
		Hyphomicrobium X for the Detection of Methanol", Division of Biochemistry and Molecular		
		Biology, School of Life Sciences, Faculty of Science, The Australian National University,		
		Canberra, Australia, Volume 30, No. 3, July 1993		
		BANDO et al., "Effects of Newly Developed Solutions Containing Trehalose on Twenty-hour		
		Canine Lung Preservation", Department of Thoracic Surgery, Chest Disease Research Institute,		
		Kyoto University, Kyoto, Japan, Volume 108, Number 1, pages 92-98, July 1994		
		BANDO et al., "Twenty-Hour Canine Lung Preservation Using Newly Developed Solutions		
		Containing Trehalose", Transplantation Proceedings, Volume 26, No. 2, pages 871-872, April		
		1994		
•		BATESON et al., "Electrokinetic Properties of Human Cryopreserved Platelets", proceeds from		
		Clinical Chemistry Department, Guy's Hospital, London; Department of Cell Biology and		
		Biochemistry, Hunterian Institute, Royal College of Surgeons, pages 213-219, 1994		
		BEATTIE et al., "Trehalose: A Cryoprotectant that Enhances Recovery and Preserves Function of		
		Human Pancreatic Islets after Long-term Storage," Diabetes, 46, pp. 519-523 (1997)		
		BLAJCHMAN et al., "The Contribution of the Haematocrit to Thrombocytopenic Bleeding in		
		Experimental Animals", Departments of Pathology and Medicine, McMaster university and the		
		Canadian Red Cross Society, Ontario, Canada, British Journal of Haematology 86, pages 347-350,		
		1994		
		BLAKELEY et al., "Dry Instant Blood Typing Plate for Bedside Use", The Lancet 336, pages		
		854-55, 1990		
Examiner	<u> </u>	Date Considered		
				

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

TECH CENTER 1600/2900

_		
PTO 1449 (Modified)	ATTORNEY DOCKET NO.	SERIAL NO.
9 IRAC	010023-000130US	10/052,162
LIST OF PATENTS AND PUBLICATIONS	APPLICANT:	GROUP ART UNIT:
FOR APPLICANT'S INFORMATION	CROWE et al.	1632
DISCLOSURE STATEMENT	FILING DATE:	
(Use Several Sheets if Necessary)	January 16, 2002	Page 3 of 6

OTHER ART

Examiner's Initials	Cite No.	Include Author, Title, Date, Pertinent Pages, Etc.	
Initials			
IIIIIIII		·	
,		BOCK et al., "Cryopreservation of Human Platelets with Dimethyl Sulfoxide: Changes in	
		Biochemistry and Cell Function", Department of Transfusion Medicine, University of Magdeburg,	
		Magdeburg, Germany and the Transfusion Center, Klinikum Grosshadern, University of Munich,	
		Transfusion 35, pages 921-924, 1995	
		BODE et al., "Sustained Elevation of Intracellular Cyclic 3'-5' Adenosine Monophosphate is	
		Necessary for Preservation of Platelet Integrity During Long-Term Storage at 22°C", Departments	
.		of Pathology and Laboratory Medicine and Surgery, East Carolina University School of Medicine,	
		Volume 83, No. 5, pages 1235-1243, March 1994	
		BODE et al. "The Use of Thrombin Inhibitors and Aprotinin in the Preservation of Platelets Stored	
•		for Transfusion", Department of Clinical Pathology and Diagnostic Medicine, East Carolina	
		University School of Medicine, pages 753-758, June 1989	
		COLACO et al., "Extraordinary Stability of Enzymes Dried in Trehalose: Simplified Molecular	
		Biology", Quadrance Research Foundation, Biotechnology Volume 10, pages 1007-1011,	
		September 1992	
		COLACO et al., "Trehalose Stabilisation of Biological Molecules", Quadrant Research	
		Foundation, Biotechnology International, pages 345-350,	
	-	CARPENTER et al., "Cryoprotection of Phosphofructokinase with Organic Solutes:	
		Characterization of Enhanced Protection in the Presence of Divalent Cations", Department of	
		Zoology, University of California, Davis, Archives of Biochemistry and Biophysics, Volume 25	
		No. 2, pages 505-512, November, 1986	
		CHAO et al., "Infusible Platelet Membrane Microvesicles: A Potential Transfusion Substitute for	
		Platelets", Transfusion, Volume 36 No. 6, pages 536-542, 1996	
		COLVIN et al., "Effect of Dry Heating of Coagulation Factor Concentrates at 80°C for 72 Hours	
		on Transmission of Non-A, Non-B Hepatitis" The Lancet, pages 814-816, October, 1988	
		CROOK et al., "Platelet Surface Charge Heterogeneity: Characterization of Human Platelet	
		Subpopulations Separated by High Voltage Continuous Flow Electrophoresis", British Journal of	
		Haematology 69, pages 265-273, 1988	
		CROWE et al., "Anhydrobiosis," Annu. Rev. Physiol., 54 pp. 579-599 (1992)	
-		CROWE et al., "Are Freezing and Dehydration Similar Stress Vectors? A Comparison of Modes	
		of Interaction of Stabilizing Solutes with Biomolecules", Symposium on Cryosensitizing and	
		Cryoprotective Agents at the 26 th Annual Meeting of the Society for Cryobiology, 27, pages 219-	
		231, 1990	
_		CROWE et al., "Cryoprotection of Phosphofructokinase with Organic Solutes: Characterization of	
		Enhanced Protection in the Presence of Divalent Cations:, Department of Zoology, University of	
.		California, Davis, Archives of Biochemistry and Biophysics, Volume 250, No. 2, pages 505-512,	
		November 1986	
		CROWE et al., "Is Vitrification Involved in Depression of the Phase Transition Temperature in	
		Dry Phospholipids?", Biochimica et Biophysica Acta (BBA) 1280, pages 187-196, 1996	
		CROWE et al., "Preservation of Liposomes by Freeze-Drying" Liposome Technology, Volume 1,	
		Chapter 14, pages 229-252, 1993	
Examiner		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

(Information Disclosure Statement—Section 9 PTO-1449 (Modified)

OCT 3 1 2003 TECH <u>CENTER</u> 1600/2900

NCT 2 7 2003 ~		POLICENIER
PTO 1449 (Modified)	ATTORNEY DOCKET NO.	SERIAL NO.
All the second s	010023-000130US	10/052,162
LIST OF PATENTS AND PUBLICATIONS	APPLICANT:	GROUP ART UNIT:
FOR APPLICANT'S INFORMATION	CROWE et al.	1632
DISCLOSURE STATEMENT	FILING DATE:	
(Use Several Sheets if Necessary)	January 16, 2002	Page 4 of 6

OTHER ART

		OTHE	K AR I
Examiner's	Cite No.	Include Author, Title, Date, Pertinen	t Pages, Etc.
Initials			
		CROWE et al., "Preservation of Mer	nbranes in Anhydrobiotic Organisms: The Role of
		Trehalose", American Association fo	or the Advancement of Science, Volume 223, pages 701-703,
		February, 1984	
			ctural and Functional Activity in Lyophilized Sarcoplasmic
		Reticulum", Archives of Biochemist	ry and Biophysics, Volume 220, No. 2, pages 477-484,
		February 1983	
			lrates on Membrane Stability at Low Water Activities",
		Department of Zoology, University	of California, Davis, Biochemica et Biophysica Acta, 769,
		page4s 141-150, 1984	
		,	eze-Dried Liposomes by Trehalose", Department of Zoology,
		University of California, Davis, Arch	nives of Biochemistry and Biophysics, Volume 242, No. 1,
		pages 240-247, October, 1985	
		DALE et al, "High-Efficiency Entrap	oment of Enzymes in Resealed Red Cell Ghosts by Dialysis",
			zymology, Volume 149, pages 229-234, 1987
			Goodman & Gilman's The Pharmacological Basis of
		Therapeutics," 9th Edition, McGraw-	
		ELEUTHERIO Elis C.A., "Role of t	he Trehalose Carrier in Dehydration Resistance of
		Saccharomyces Cerevisiae", Biochir	nica et Biophysica Acta, 1156, pages 263-266, 1993
			matozoa Frozen in Whole Milk Extender with Trehalose,
			ent of Animal Science Cornell University and Eastern
		-	Inc., Ithaca, New York, Journal of Dairy Science, Volume 76,
		No. 7, 1993	
GERENCSER, George A., "Cryoprotection of Aplysia Gut Basolateral Memb Trehalose", Department of Physiology, College of Medicine, University of Fl			
		Biochem. Physiol. Volume 108A, No	
-			Metabolic Activity in Lyophilized Human Erythrocytes",
		Proc. Natl. Acad. Sci. Volume 89, pa	
			e in Canine Lung Preservation", Department of Thoracic
			titute, Kyoto University, Kyoto, Japan, Volume 115, Number
		1, pages 102-107, January 1994	
		1	e in Preservation of Canine Lung for Transplants",
Department of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, K			
		Japan, Thorac. Cardiovasc. Surgeon	
	HIRATA et al., "Successful 12-Hour Lung Preservation with Trehalose", Transplantation		
		Proceedings, Volume 25, No. 1, page	
		HOLME et al., "Evaluation of Platelet Concentrates Stored for 5 days with Reduced Plasma	
		Volume", American Red Cross, Mid-Atlantic Region and Eastern Virginia Medical School,	
		Transfusion, Volume 34, No. 1, page	
			nce of Platelet in vivo Viability During Storage When Using a
			American Red Cross, East Carolina University School of
		Medicine, Volume 119, No. 2, pages	
Examiner			Date Considered
		Į.	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

OCT 3 1 2003 .

TECH OFM

		USUH CENTED 10
PTO 1449 (Modified)	ATTORNEY DOCKET NO.	SERIAL NO.
Te man Pate	010023-000130US	10/052,162
LIST OF PATENTS AND PUBLICATIONS	APPLICANT:	GROUP ART UNIT:
FOR APPLICANT'S INFORMATION	CROWE et al.	1632
DISCLOSURE STATEMENT	FILING DATE:	
(Use Several Sheets if Necessary)	January 16, 2002	Page 5 of 6

OTHER ART

		OTHER ART
Examiner's	Cite No.	Include Author, Title, Date, Pertinent Pages, Etc.
Initials		,
•		HOTTIGER et al., "The Role of Trehalose Synthesis for the Acquisition of Thermotolerance in
		Yeast II. Physiological Concentrations of Trehalose Increase the Thermal Stability of Protein In
		Vitro", Eur. J. Biochem. 219, pages 187-193, 1994
		HUGHES et al., "Reversibly Electropermeabilized Platelets: Potential Use as Vehicles for Drug
		Delivery", Department of Biochemistry, Hunterian Institute, Royal College of Surgeons of
		England, Biochemical Society Transactions, pages 871-873, March 1990
		HUGHES et al., "Reversible Electropermeabilisation of Human and Rat Blood Platelets:
		Evaluation of Morphological and Functional Integrity 'In Vitro' and 'In Vivo'", Department of
		Biochemistry and Cell Biology, Hunterian Institute, Royal College of Surgeon of England,
		Biochimica et Biophysica Acta, 981, pages 277-287, 1989
		IHLER et al., "Hypotonic Hemolysis Methods for Entrapment of Agents in Resealed
		Erythrocytes", Methods of Enzymology, Volume 149, pages 221-229, 1987
		JINDAL et al., "Preservation and Storage of Pancreatic Islets", Division of Transplantation, Mt.
		Sinai School of Medicine, New York and University of Oxford, United Kingdom, Vol. 57, pages
		317-321, No. 3, February 1994
		LESLIE et al., "Trehalose and Sucrose Protect Both Membranes and proteins in Intact Bacteria
		during Drying", Section of Molecular and Cellular Biology, University of California, Davis,
		Applied and Environmental Microbiology, pages 3592-3597, October, 1995
	 	LESLIE et al., "Trehalose Lowers Membrane Phase Transitions in Dry Yeast Cells," Biochimica
		et Biophysica Acta, 1192, pp. 7-13 (1994)
	 	LIONETTI et al., "Improved Method for the Cryopreservation of Human Red Cells in Liquid
		Nitrogen with Hydroxythyl Starch", Center for Blood Research and Tufts University School of
		Medicine, Boston, MA, Cryobiology13, pages 489-499, 1976
•		MAGNANI et al., "Targeting Antiretroviral Nucleoside Analogues in Phosphorylated Form to
		Macrophages: In Vitro and In Vivo Studies", Proc. Natl. Acad. Sci., Volume 89, pages 6477-6481,
		July 1992
		MOROFF et al., "Effect on Platelet Properties of Exposure to Temperatures Below 20°C for Short
		Periods During Storage at 20 to 24°C", American Red Cross, Jerome H. Holland Laboratory for
		the Biomedical Sciences, and Red Cross Blood Services, Transfusion, Volume 34, No. 4, pages
		317-321, 1994
		OKADA et al., "Introduction of Macromolecules into Cultured Mammalian Cells by Osmotic
		Lysis of Pinocytic Vesicles", Department of Biology, University of Utah, Volume 29, pages 33-
		41, May 1982
	1	OWNERS et al., "The Role of Platelet Microparticles in Hemostasis," Transfusion Medicine
		Reviews, 8 (1) pp. 37-44 (1994)
		PUISIEUX et al., "Liposomes, New Systems and New Trends in their Applications", Published in
		France by Editions de Sante, Chapter 8, pages 239-272, 1995
·	†	RAYOS et al., "Quick Freezing of Unfertilized Mouse Oocytes Using Ethylene Glycol with
		Sucros or Trehalose", Department of Theriogenology, Faculty of Veterinary Medicine, Hokkaido
		University, Japan, Journal of Reproduction and Fertility, pages 123-129, March 1993
		READ et al., "Preservation of Hemostatic and Structural Properties of Rehydrated Lyophilized
		Platelets: Potential for Long-Term Storage of Dried Platelets for Transfusion", Proc. Natl. Acad.
		Sci, Volume 92, pages 397-401, January 1995
Examiner	1.	Date Considered

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

OCT 3 1 2003 TECH CENTER 1600/290(SERIAL NO. ATTORNEY DOCKET NO. 010023-000130US 10/052,162 APPLICANT: **GROUP ART UNIT:** CROWE et al. 1632 FILING DATE:

Page 6 of 6

PTO 1449 (Modified TRADE) LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT

(Use Several Sheets if Necessary)

OTHER ART

January 16, 2002

		OTHER ART	
Examiner's Initials	Cite No.	Include Author, Title, Date, Pertinent Pages, Etc.	
		RECHSTEINER, Martin, "Osmotic Lysis of Pinosomes", Methods in Enzymology, Volume 149, pages 42-48, 1987	
		ROSER et al., "A Sweeter Way to Fresher Food", New Scientist, May 1993	
		ROSER, Bruce, "Trehalose, a New Approach to Premium Dried Foods", Trends in Food Science & Technology, July 1991	
		RUDOLPH et al., "A Calorimetric and Infrared Spectroscopic Study of the Stabilizing Solute Proline", Biophysical Society, Volume 50, pages 423-430, September 1986	
		SHIER, W. Thomas, "Studies on the Mechanisms of Mammalian Cell Killing by a Freeze-Thaw Cycle: Conditions that Prevent Cell Killing Using Nucleated Freezing", Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Minnesota, Cryobiology 25, pages 110-120 (1988)	
		TABLIN et al., "Membrane Phase Transition of Intact Human Platelets: Correlation with Cold-Induced Activation", Departments of Anatomy, Physiology, and Cell Biology and Molecular and Cellular Biology, University of California, Davis, Journal of Cellular Physiology 168, pages 305-313, 1996	
		TERASAKI et al., "Localization of endoplasmic Reticulum in Living and Glutaraldehyde-Fixed Cells with Fluorescent Dyes", Dana-Farber Cancer Institute and Department of Pathology Harvard Medical School, Cell, Volume 38, pages 101-108, August 1984	
		VALERI et al., "A Simple Method of Freezing Human Platelets Using 6% Dimehtylsulfoxide and Storage at -80°C," <i>Blood</i> , 43 (1) pp. 131-136 (1974)	
		VERMA et al., "Gene Therapy – Promises, Problems and Prospects," <i>Nature</i> , Vol. 389, pp. 239-242, September 18, 1997	
		YOKOMISE et al., "Reliable Cryopreservation of Trachea for One Month in a New Trehalose Solution", Division of Thoracic Surgery, Chest Disease Research Institute, Kyoto University, Kyoto, Japan, Volume 110, Number 2, pages 382-385, 1995	
Examiner		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant(s).

(Information Disclosure Statement—Section 9 PTO-1449 (Modified)